Review Article

Prevalence and Severity of Ocular Surface Neoplasia in African Nations and Need for Early Interventions

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Abstract

Ocular surface squamous neoplasia (OSSN) is a common ocular surface tumor with an increased incidence in African countries (3.4 and 3.0 cases/year/100,000). Despite its potential for vision loss and death, OSSN remains largely neglected by both eye and HIV care programs in Africa. The purpose of this review is to identify the barriers to timely diagnosis and early interventions for OSSN in Africa. PubMed searches were conducted targeting previous use of topical chemotherapy (interferon alpha 2b, Mitomycin-C, 5-Fluorouracil) and Human papillomavirus (HPV) vaccination in Africa. We found that OSSN is a significant vision and life-threatening health problem in Africa leading to significant loss of vision, as well as facial disfigurement and social stigma. We did not find any reports on the use of topical interferon, Mitomycin-C or HPV vaccination for OSSN in Africa. One report on the use of topical 5-FU for OSSN in Africa was found. Common barriers to early detection and management of OSSN in Africa include lack of sufficient laboratory infrastructure, lack of trained healthcare personnel, lack of compliance with follow-up visits, cost of topical chemotherapies, and cultural preferences for traditional medicines. In conclusion, OSSN is a significant vision and life-threatening health problem in Africa. There is not much literature on prevention or treatment options for early stages of OSSN in Africa. The use of topical chemotherapy as early interventions and judicious use of smart phone Apps to help with remote diagnosis of early OSSN should be further explored.

Keywords: Africa; HIV; Ocular Surface Squamous Neoplasia; Topical Chemotherapy

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INTRODUCTION

Ocular surface squamous neoplasia (OSSN), the most common ocular surface tumor, refers to a spectrum of lesions ranging from dysplasia, intraepithelial neoplasia and carcinoma *in situ* to invasive squamous cell carcinomas.[1] It appears clinically as a flesh-like elevation with a gelatinous, leukoplakic or papilloform appearance [Figure 1].[1] It is often found near the limbus [Figure 2] and can affect both the cornea and conjunctiva but can also involve the palpebral and tarsal conjunctiva [Figure 3] and if untreated and in advanced stages can invade the orbit.[1]

The incidence of OSSN is difficult to determine and varies geographically, yet shows noticeably increased rates in Africa.[1] A recent study in Zimbabwe by Gichuhi et al showed an incidence rate of

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3.4 and 3.0 cases/year/100,000 for males and females, respectively.[2] This contrasts with the worldwide rate of 0.18 and 0.08 cases/year/100,000 for males and females respectively.[2]

The main risk factors for OSSN are ultraviolet (UV) exposure,[1] human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS),[1] and human papilloma virus (HPV) infection.[1] These risk factors are increasing in African countries and are believed to be the major causes of the increased incidence rates observed.[1] The risk for local invasion and distant metastasis of OSSN in general is low, but increases in patients with these risk factors.[1]

Despite its high prevalence in African countries, OSSN remains largely neglected by both eye and HIV care programs in Africa.[3] This is mostly due to the fact that OSSN often does not affect vision in early stages, and many of these programs focus on preventable blindness issues.[3] Yet there are compelling reasons to suggest the need for early treatment of OSSN in Africa.[3] In later stages, OSSN can lead to blindness as well as facial disfigurement and death.[3] Patients are often left with major orbitofacial defects and poor cosmetic outcomes after being treated for advanced disease, leading to social discomfort and limited social interaction.[2,4] This is compounded by the fact that there are often limited or no expertise or facilities to provide reconstructive surgery or orbital prosthesis in poor countries such as those in Africa.[3]

A further consideration is that, with the introduction of highly active retroviral therapy (HAART) for HIV infected patients, overall quality of life and survival of HIV infected individuals has improved.[3] But the unsightly appearance of advanced squamous cell carcinoma (SCC) of the orbital and facial areas frequently associated with HIV infection in African populations, can "unmask" an otherwise "hidden" HIV infection in these individuals, exposing them to the discrimination that comes with HIV infection.[3] Further, as untreated SCC threatens survival, failing to make efforts to prevent this from occurring compromises the gains from HAART in HIV-infected individuals.[3]

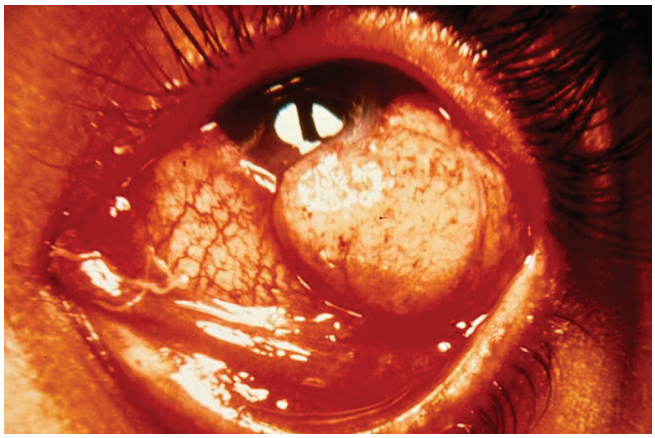

Figure 1. Slit lamp photo demonstrates typical squamous carcinoma involving the conjunctiva and cornea.

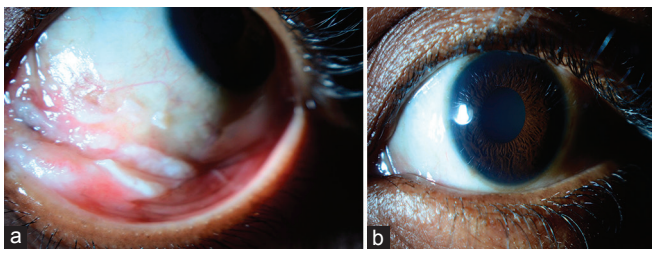

Figure 3. (a) OSSN (Squamous carcinoma *in situ* in this case) of the palpebral and tarsal conjunctiva in an African American patient. (b) This lesion was masked because of normal appearing skin of the eyelid and the lower eyelid completely covered the lesion. This case highlights the importance of careful inspection of the upper and lower eyelid fornices and eversion of the upper eyelid to find lesions that may be under the upper eyelid or inside the lower eyelid.

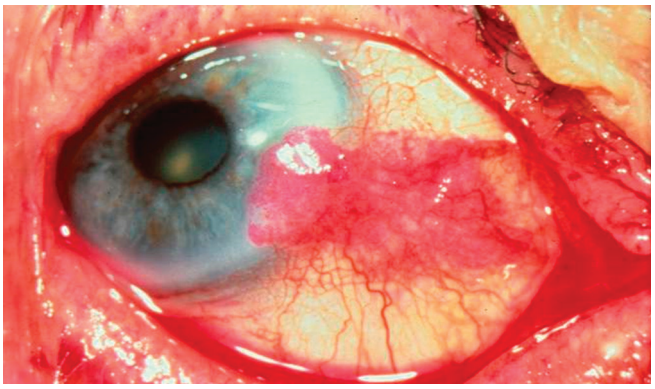

Figure 2. Slit lamp photograph of an earlier (less advanced lesion) stained with Rose Bengal stain.

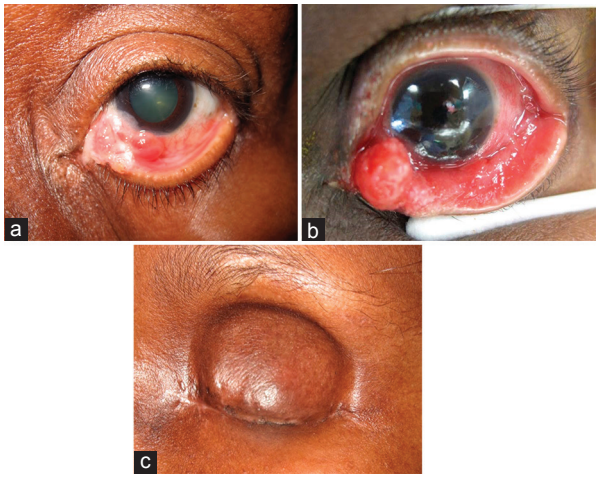

Figure 4. (a and b) Slit lamp photographs in another African American patient with recurrent squamous carcinoma of the conjunctiva and cornea involving large parts of the ocular surface and lower eyelid. This patient eventually needed an orbital exenteration due to lack of response to all other treatments and poor compliance with follow up visits. (c) Facial appearance after an orbital exenteration.

Like many diseases, the best option for controlling OSSN remains early detection and intervention. More advanced stages of disease require more expensive treatments and would lead to the need for referral to tertiary care centers and such delays in diagnosis and management are generally associated with worse overall outcomes [Figure 4].[3] Therefore, it is important to focus on early diagnosis and interventions, particularly in countries with limited resources such as African countries.[3]

Current treatment options for OSSN include surgical excision, topical chemotherapy, cryotherapy and less commonly brachytherapy.[3] Surgical excision remains the most definitive option, yet in African countries with limited access to surgical facilities, other treatment options need to be explored.[3]

Potential alternatives to surgery and options for early intervention include topical chemotherapy using 5-FU drops, interferon alpha 2b drops, or mitomycin C drops.[3] These topical treatments could be packaged in small vials and do not require strict conditions for storage except perhaps refrigeration for topical interferon.[3]

While topical chemotherapies present a possible treatment option in Africa, as of now they are not readily available in these countries.[3] Additionally, specific studies of their efficacy in African populations are currently lacking.[1] A recent review by Gichuhi and Irlam concluded that there are no randomized controlled trials of interventions currently used against OSSN in HIV-infected individuals, and that current clinical practice rests on a weak evidence based on small case series and case reports.[3]

Another possible treatment strategy for OSSN would be human papilloma virus (HPV) vaccination as a means of preventing OSSN, yet the relationship between HPV and OSSN remains controversial.[2] A review of 12 case series and 17 case-control studies showed no causal relationship between mucosal types of HPV and OSSN, while the association with cutaneous types was uncertain.[2] A meta-analysis of case-control studies showed association of HPV and OSSN in sub-Saharan Africa (pooled OR = 2.64, 95% CI: 1.27-5.49) and worldwide (pooled OR = 4.00, 95% CI: 2.11-7.57).[2] Depending on the geographic region, the prevalence of HPV in OSSN ranges from 0% to 100%, with most African studies reporting a prevalence of 75%-85%.[2] While the increased prevalence in African countries appears promising for HPV vaccination as a means to prevent OSSN, further research is needed to confirm the association of OSSN and HPV infection, as well as to determine which specific subtypes are involved, before widespread vaccination efforts can be justified.[2]

In this review, we evaluate all publications to date specifically on HIV-related OSSN and SCC of conjunctiva and orbit in African countries with the purpose of identifying barriers and limitations to early interventions and prevention of OSSN. We specifically searched for existing literature on early intervention and prevention strategies targeted towards ocular surface squamous neoplasia in African countries with the aim to identify potential areas for future research, education and intervention.

METHODS

PubMed searches were conducted targeting previous use of topical chemotherapy (interferon, mitomycin-C, 5-FU) and HPV vaccination in African countries, both in general and for the specific use of OSSN.

We also searched the literature for common limitations and barriers encountered during the diagnosis and treatment of OSSN in underdeveloped countries. These limitations will be discussed along with potential solutions for overcoming these barriers.

RESULTS

There are no reports published on the use of topical interferon, mitomycin-C, or HPV vaccination for OSSN in Africa [Table 1]. One paper was found on the use of topical 5-FU for OSSN in Africa.

A search for publications on the use of topical chemotherapy or HPV vaccination in countries other than Africa yielded the following publications: topical interferon use in OSSN (34 papers), topical 5-FU for OSSN (19 papers), topical mitomycin-C for OSSN (52 papers), and association between HPV and OSSN (19 papers). For uses other than OSSN in Africa, significant literature exists on the use of topical interferon

Table 1. PubMed Search Results for literature on diagnosis and management of OSSN in Africa

Search criteria	Hits
Africa + ocular surface squamous neoplasia + prevention	0
Africa + ocular surface squamous neoplasia + detection	0
Africa + ocular surface squamous neoplasia + diagnosis	15
Africa + ocular surface squamous neoplasia + intervention	0
Africa + ocular surface squamous neoplasia + treatment	10
Africa + ocular surface squamous neoplasia + management	6
ocular surface squamous neoplasia + prevention	12
ocular surface squamous neoplasia + detection	5
ocular surface squamous neoplasia + diagnosis	196
ocular surface squamous neoplasia + intervention	10
ocular surface squamous neoplasia + treatment	167
ocular surface squamous neoplasia + management	52
Africa (title) + barrier (title)	8

(1276 papers), HPV vaccine (780 papers), topical 5-FU (93 papers), and topical mitomycin-C (47 papers).

We found one previous study by Gichuhi and Irlam, published in 2013, which found that no randomized controlled trials exist for interventions against OSSN of the conjunctiva in individuals with HIV.[3] One ongoing randomized controlled trial in Kenya was registered but was incomplete at the time of Gichuhi's and Irlam publication.[3]

While conducting our literature review we identified several limitations and barriers to the early diagnosis and treatment of OSSN in Africa.

Summary of Limitations and Barriers to Diagnosis and Treatment of OSSN in Africa

Lack of sufficient laboratory infrastructure and personnel was reported as a limitation frequently encountered in Africa in several studies.[5,6] In a paper by Nutt et al, the authors concluded that the lack of histopathology or cytology services leads to the inability to make the correct diagnosis of OSSN, which not only prevents early and accurate detection of disease, but also reduces the ability to analyze the effectiveness of OSSN treatments.[6]

Several reports suggest that lack of compliance with recommended follow-up visits is a big problem in African nations.[6,7] This is a challenge because of the long distances to travel for consultations, and thus patients are unlikely to come back for treatment for something like OSSN unless it is in its advanced stages significantly impacting their quality of life, at which point early interventions are no longer possible.[6,8] A 2010 study in Tanzania showed that 40% of operated suspected OSSN cases were managed outside of major hospitals where better facilities and quality of care was available, because of difficulty of traveling to and accessing these centers.[5] In response to this issue, the same study described training that was provided for the recognition, referral, and reporting of OSSN for eye health care workers outside of major hospitals.[5] Training included the explanation and demonstration of the differences in typical clinical appearances of various lesions such as OSSN.[5] Importantly, workers were trained to know when to refer cases of suspected OSSN for excisional biopsy.[5] Finally, if traveling to a referral hospital was not possible, they were trained on the excision of lesions with wide surgical margins.[5]

The cost of interventions for early treatment of OSSN may be prohibitive when considering their use in African countries.[9] Thus, affordability is a major consideration when comparing various topical chemotherapy options for OSSN. Interferon is a very effective and well-tolerated form of treatment for early OSSN; drops are used daily and work slowly but very effectively and have been reported to be associated with 67-100% response rate for OSSN in HIV or non-HIV patients.[10-17] However, interferon is more expensive when compared to other topical chemotherapy options. The cost of topical interferon is $300 per treatment compared to $150 per treatment for mitomycin- C and $100 per treatment for 5-FU.[18] A recent study in Angola provided 5-FU treatment (1% solution four times a day for 7 days) for a cost of $1 USD per treatment cycle, supporting the idea that 5-FU may be a much more economical treatment option in terms of cost in Africa.[6]

Even if treatment options were readily available to African patients with OSSN, cultural and religious preferences for traditional medicines and/or alternative remedies might limit compliance.[19] There is a long history of traditional medicine linked to strong cultural values and belief systems.[19] Practitioners of Western-style medicine often view these traditional practices unfavorably due to the lack of evidence of safety and efficacy; patients know this and may conceal their use of traditional remedies due to the fear of being ridiculed.[19] For example, a study in Zambia reported two patients who abandoned anti-retroviral therapy in favor of a local herbal remedy, and another who sought to cure his disease through prayer.[19] Patients are also taking measures to falsely convince health care professionals of their continued adherence to prescribed medications.[19] There is also skepticism regarding HIV care both among patients and within communities; for example regional governments have often called for an "African" solution to the epidemic rather than "Western" solutions.[19]

To address these cultural barriers, Reid et al proposed targeted education campaigns to address issues directly within communities with leadership from individual governments as well as from national and international health bodies.[19] The authors advocated for stronger collaboration between traditional and Western-style health practitioners, with patient-centered adherence counseling with non-judgmental approaches to traditional (non-Western) medical practices.[19]

Alternate Screening Options

Several alternate diagnostic options for OSSN, other than clinical features or histopathology, are available. These include the use of stains such as toluidine blue 0.05% and methylene blue or imaging techniques such as confocal microscopy.

A recent study in Kenya evaluated the accuracy of using toluidine blue 0.05% ocular surface staining to reliably differentiate OSSN from benign conjunctival lesions.[20] 419 adult patients underwent comprehensive ophthalmic examination including slit lamp biomicroscopy that included ocular surface staining with toluidine blue 0.05%.[20] Photographs were taken of lesions with and without staining, and masked examiners reviewed 100 consecutive photographs.[20] The authors reported that toluidine blue 0.05% had a high sensitivity (92%) but

low specificity (31%) for diagnosis of OSSN compared to confirmation by histopathology.[20] The authors conclude that toluidine blue staining may be a good screening tool but not a good diagnostic tool for OSSN due to the frequency of false-positives.[20]

Authors have also evaluated the use of toluidine blue 1%, a different concentration than just discussed, in diagnosing OSSN.[21] The authors found that the dye stained 100% of OSSN and 90% of pre-malignant lesions.[21] One patient with a benign lesion showed a positive staining.[21]

A similar study was conducted to evaluate the use of ocular surface staining with methylene blue in patients with suspicious conjunctival lesions.[22] The authors found that staining with methylene blue had a similar high sensitivity (97%) and low specificity (50%) in diagnosing OSSN.[22]

In vivo confocal microscopy analysis of the cytological characteristics of OSSN represents another screening option.[23] This is a safe, effective, relatively non-invasive and painless method that can be performed in regular office settings, and would be good for patients who refuse more invasive surgery.[23] It could be used as a diagnostic method or for distinguishing the different subtypes of OSSN, estimation of recurrence, and evaluation of response to topical chemotherapies.[23] However, it requires availability of expensive technology likely not available in the field or outside major tertiary centers, and remains somewhat investigational as a diagnostic method.[23] Another limitation of *in vivo* confocal microscopy is that the maximum examining depth is 500 μm, so it would be unable to detect tumors that may invade the eye or orbit.[23]

Some authors have proposed impression cytology as a potentially useful screening option.[24] Through the use of a cellulose filter applied directly to a lesion on the ocular surface, it is possible to obtain cytology without the need for more invasive intervention.[24] For diagnosing OSSN, a high positive predictive value was reported for impression cytology compared with tissue histology but a 53% negative predictive value was noticed, indicating that a significant number of malignant lesions would be missed on impression cytology.[24]

DISCUSSION

Our review suggests that there are a variety of complex barriers to management of OSSN in African countries, including limitations in screening, diagnosis, and treatment. Issues with screening and early detection primarily stem from a lack of infrastructure for ophthalmic examination and trained professionals with familiarity with clinical features that suggest malignancy versus a benign lesion. The biggest limitation is the small number of trained surgeons and pathologists in African countries to surgically manage OSSN.

Since early detection of OSSN can lead to less invasive treatments such as topical chemotherapy and better visual and quality of life outcomes, there is a need to educate health professionals in remote areas on the differences between benign and malignant ocular surface lesions and common clinical features of OSSN. This may include looking for signs that are more prevalent in malignant cases, such as feeder vessels, gelatinous appearance and leukoplakia [Figure 1].[8,18] These signs as well as others could be used to help develop a diagnostic algorithm, as proposed by Nguena et al, to help clinicians identify OSSN and know when to appropriately refer for more specialized care.[8] Tumor depth could also provide a simple clinical measure to use in order to differentiate between high risk OSSN and benign lesions.[25] Male gender and HIV seropositivity could also be incorporated into the algorithm.[25] Clinicians should also be made aware of the link between OSSN and HIV and actively monitor HIV-infected patients for OSSN in order to diagnose and initiate treatments as early as possible.[26]

The lack of trained examiners underscores the potential utility of adjunct clinical examination techniques, such as ocular surface staining with toluidine blue 0.05% or 1% or methylene blue, or imaging with confocal microscopy. It appears that collectively these techniques, with their high sensitivity, may be useful in a screening setting and increase the suspicion of malignancy in the event of positive staining.

Future funding should focus on the infrastructure needed for pathology labs as well as appropriate personnel, both in major hospital systems and in smaller, local health centers. Distance traveled for appropriate care is also a commonly identified issue for patients in Africa. As travel is likely to remain difficult for patients, a means to improve patient transportation and/or a focus on training eye health field workers outside of major hospitals (in centers more accessible to patients) will be important.

In remote areas where the appropriate infrastructure is unlikely to become available, there may be a role for telemedicine. As suggested by Nguena et al, there is a need to educate health professionals in remote areas and to develop a simple-to-follow algorithm to aid in the accurate diagnosis of OSSN.[8] The use of smart phone applications that are available in ophthalmology to transmit images from the field to the referral centers would be another way to improve early diagnosis of OSSN. These applications have been shown to safely and effectively diagnose various ophthalmic conditions ranging from the anterior segment to the posterior segment, including visualization of the optic nerve and even detailed measurements of toric intraocular lens alignment.[27-29] Use of smart phone technology would provide a user-friendly and accessible way for health professionals in remote settings to transmit images for second opinions and to more rapidly and accurately

diagnose OSSN. These strategies can hopefully lead to earlier diagnosis and earlier, less invasive interventions for OSSN, particularly in places such as East Africa where there is limited access to specialists.[8]

Our review suggests a lack of utilization of topical chemotherapy to treat OSSN in Africa. Topical therapies, particularly topical interferon, have been shown to be effective and well-tolerated, yet issues such as cost and need for refrigeration continue to prevent their use in Africa. One issue unique to African countries may be lack of access to refrigeration required for storage of drugs such as topical interferon. One potential solution is to invest in small portable coolers that could even be worn around the neck or carried in the pocket to improve the feasibility and transportation of the topical interferon drops. Alternatively, topical drugs that do not require refrigeration, such as topical 5-FU, can be considered as early intervention for OSSN; however, topical 5-FU is associated with more significant ocular surface toxicity and thus would require more frequent monitoring of patients while it is being administered.[30-33]

Our review also suggests that, with the exception of one report on 5-FU, no literature exists on the use of topical chemotherapy such as topical interferon, 5-FU, or MMC or HPV vaccination as a means of early intervention or prevention of OSSN in Africa. Thus there is a definite need for further studies of such treatment options for less advanced OSSN specifically in patients in African countries.

Finally, given that ultraviolet exposure is considered a risk factor for OSSN and as exposure to sunlight remains a major risk for people in Africa, simple interventions to reduce UV exposure could be implemented in African countries, such as using sunglasses that filter UV light,[26] and wearing appropriate clothing, hats, or UV blocking contact lenses for additional UV protection.[34]

In conclusion, OSSN is a significant vision and life threatening health problem in Africa. Early intervention can help prevent loss of the eye, facial disfigurement, and social stigma due to advanced presentation of disease. There is not much literature on early detection and treatment options for early stages of OSSN in Africa. Some of the barriers encountered for early diagnosis and early treatment of OSSN in Africa include lack of availability of trained health care workers in the field, lack of familiarity of primary care physicians and oncologists with signs and symptoms of early OSSN, and limited access to topical chemotherapies. Potential solutions to overcome these barriers in the future should focus on developing smart phone Apps that will help with remote diagnosis of early OSSN, and development of portable cooling devices to administer topical chemotherapy to African patients with early stages of OSSN, particularly those with HIV.

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Conflicts of Interest

There are no conflicts of interest.

REFERENCES

1. Kheir WJ, Tetzlaff MT, Pfeiffer ML, Mulay K, Ozgur O, Morrell G, et al Epithelial, non-melanocytic and melanocytic proliferations of the ocular surface. *Semin Diagn Pathol* 2016;33:122-132.
2. Gichuhi S, Sagoo MS, Weiss HA, Burton MJ. Epidemiology of ocular surface squamous neoplasia in Africa. *Trop Med Int Health* 2013;18:1424-1443.
3. Gichuhi S, Irlam JH. Interventions for squamous cell carcinoma of the conjunctiva in HIV-infected individuals. *Cochrane Database Syst Rev* 2013;2:CD005643.
4. Bonanno A, Esmaeli B, Fingeret MC, Nelson DV, Weber RS. Social challenges of cancer patients with orbitofacial disfigurement. *Ophthal Plast Reconstr Surg* 2010;26:18-22.
5. Furahini G, Lewallen S. Epidemiology and management of ocular surface squamous neoplasia in Tanzania. *Ophthalmic Epidemiol* 2010;17:171-176.
6. Nutt RJ, Clements JL, Dean WH. Ocular surface squamous neoplasia in HIV-positive and HIV-negative patients and response to 5-fluorouracil in Angola. *Clin Ophthalmol* 2014;8:2435-2440.
7. Yorston D, Khaw PT. A randomised trial of the effect of intraoperative 5-FU on the outcome of trabeculectomy in east Africa. *Br J Ophthalmol* 2001;85:1028-1030.
8. Nguena MB, van den Tweel JG, Makupa W, Hu VH, Weiss HA, Gichuhi S, et al Diagnosing ocular surface squamous neoplasia in East Africa: Case-control study of clinical and *in vivo* confocal microscopy assessment. *Ophthalmology* 2014;121:484-491.
9. Ogun GO, Ogun OA, Bekibele CO, Akang EE. Intraepithelial and invasive squamous neoplasms of the conjunctiva in Ibadan, Nigeria: A clinicopathological study of 46 cases. *Int Ophthalmol* 2009;29:401-409.
10. Kusumesh R, Ambastha A, Sinha B, Kumar R. Topical interferon a-2b as a single therapy for primary ocular surface squamous neoplasia. *Asia Pac J Ophthalmol (Phila)* 2015;4:279-282.
11. Zarei-Ghanavati S, Alizadeh R, Deng SX. Topical interferon alpha-2b for treatment of noninvasive ocular surface squamous neoplasia with 360° limbal involvement. *J Ophthalmic Vis Res* 2014;9:423-426.
12. Nanji AA, Moon CS, Galor A, Sein J, Oellers P, Karp CL. Surgical versus medical treatment of ocular surface squamous neoplasia: A comparison of recurrences and complications. *Ophthalmology* 2014;121:994-1000.
13. Shields CL, Kaliki S, Kim HJ, Al-Dahmash S, Shah SU, Lally SE, et al Interferon for ocular surface squamous neoplasia in 81 cases: Outcomes based on the American Joint Committee on Cancer classification. *Cornea* 2013;32:248-256.
14. Kim HJ, Shields CL, Shah SU, Kaliki S, Lally SE. Giant ocular surface squamous neoplasia managed with interferon alpha-2b as immunotherapy or immunoreduction. *Ophthalmology* 2012;119:938-944.
15. Shah SU, Kaliki S, Kim HJ, Lally SE, Shields JA, Shields CL. Topical interferon alfa-2b for management of ocular surface squamous neoplasia in 23 cases: Outcomes based on American Joint Committee on Cancer classification. *Arch Ophthalmol* 2012;130:159-164.
16. Karp CL, Galor A, Chhabra S, Barnes SD, Alfonso EC. Subconjunctival/perilesional recombinant interferon α2b for ocular surface squamous neoplasia: A 10-year review. *Ophthalmology* 2010;117:2241-2246.
17. Sturges A, Butt AL, Lai JE, Chodosh J. Topical interferon or surgical excision for the management of primary ocular surface squamous neoplasia. *Ophthalmology* 2008;115:1297-12302, 1302.e1.

18. Esquenazi S, Fry CL, Holley E. Treatment of biopsy proved conjunctival intraepithelial neoplasia with topical interferon alfa-2b. *Br J Ophthalmol* 2005;89:1221.
19. Reid SE, Mulenga LB, Folk WR, Tambatamba BC, Chi BH. Abandonment of antiretroviral therapy: A potential barrier to scale-up in Sub-Saharan Africa. *S Afr Med J* 2008;98:448, 450.
20. Gichuhi S, Macharia E, Kabiru J, Zindamoyen AM, Rono H, Ollando E, et al Toluidine blue 0.05% vital staining for the diagnosis of ocular surface squamous neoplasia in Kenya. *JAMA Ophthalmol* 2015;133:1314-1321.
21. Romero IL, Barros Jde N, Martins MC, Ballalai PL. The use of 1% toluidine blue eye drops in the diagnosis of ocular surface squamous neoplasia. *Cornea* 2013;32:36-39.
22. Steffen J, Rice J, Lecuona K, Carrara H. Identification of ocular surface squamous neoplasia by *in vivo* staining with methylene blue. *Br J Ophthalmol* 2014;98:13-15.
23. Xu Y, Zhou Z, Xu Y, Wang M, Liu F, Qu H, et al The clinical value of *in vivo* confocal microscopy for diagnosis of ocular surface squamous neoplasia. *Eye (Lond)* 2012;26:781-187.
24. Tananuvat N, Lertprasertsuk N, Mahanupap P, Noppanakeepong P. Role of impression cytology in diagnosis of ocular surface neoplasia. *Cornea* 2008;27:269-274.
25. Tiong T, Borooah S, Msosa J, Dean W, Smith C, Kambewa E, et al Clinicopathological review of ocular surface squamous neoplasia in Malawi. *Br J Ophthalmol* 2013;97:961-964.
26. Nagaiah G, Stotler C, Orem J, Mwanda WO, Remick SC. Ocular surface squamous neoplasia in patients with HIV infection in sub-Saharan Africa. *Curr Opin Oncol* 2010;22:437-442.
27. Bastawrous A, Giardini ME, Bolster NM, Peto T, Shah N, Livingstone IA, et al Clinical validation of a smartphone-based adapter for optic disc imaging in Kenya. *JAMA Ophthalmol* 2016;134:151-158.
28. Teichman JC, Baig K, Ahmed II. Simple technique to measure toric intraocular lens alignment and stability using a smartphone. *J Cataract Refract Surg* 2014;40:1949-1952.
29. Zvornicanin E, Zvornicanin J, Hadziefendic B. The use of smart phones in ophthalmology. *Acta Inform Med* 2014;22:206-209.
30. Rudkin AK, Dempster L, Muecke JS. Management of diffuse ocular surface squamous neoplasia: Efficacy and complications of topical chemotherapy. *Clin Experiment Ophthalmol* 2015;43:20-25.
31. Bahrami B, Greenwell T, Muecke JS. Long-term outcomes after adjunctive topical 5-flurouracil or mitomycin C for the treatment of surgically excised, localized ocular surface squamous neoplasia. *Clin Experiment Ophthalmol* 2014;42:317-322.
32. Rudkin AK, Muecke JS. Adjuvant 5-fluorouracil in the treatment of localised ocular surface squamous neoplasia. *Br J Ophthalmol* 2011;95:947-950.
33. Parrozzani R, Lazzarini D, Alemany-Rubio E, Urban F, Midena E. Topical 1% 5-fluorouracil in ocular surface squamous neoplasia: A long-term safety study. *Br J Ophthalmol* 2011;95:355-359.
34. Yam JC, Kwok AK. Ultraviolet light and ocular diseases. *Int Ophthalmol* 2014;34:383-400.